NIH RELAIS Document Delivery

NIH-10286731

JEFFDUYN

NIH -- W1 NE337

JOZEF DUYN
10 Center Dirve
Bldg. 10/Rm.1L07
Bethesda, MD 20892-1150

ATTN:
PHONE: 301-594-7305
FAX: -
E-MAIL:

SUBMITTED: 2002-08-29 17:22:17
PRINTED: 2002-09-04 06:41:47
REQUEST NO.:NIH-10286731
SENT VIA: LOAN DOC
7967416

NIH Fiche to Paper Journal

TITLE: NEUROLOGY
PUBLISHER/PLACE: Lippincott, Williams _Wilkins, Hagerstown, MD :
VOLUME/ISSUE/PAGES:1995 Jul;45(7):1384-91 1384-91
DATE: 1995
AUTHOR OF ARTICLE: Tedeschi G; Bertolino A; Righini A; Campbell G; Raman R; Duy
TITLE OF ARTICLE: Brain regional distribution pattern of metabolite
ISSN: 0028-3878
OTHER NOS/LETTERS: Library reports holding volume or year
0401060
7617201
SOURCE: PubMed
CALL NUMBER: W1 NE337
REQUESTER INFO: JEFFDUYN
DELIVERY: E-mail: jhd@helix.nih.gov
REPLY: Mail:

Brain regional distribution pattern of metabolite signal intensities in young adults by proton magnetic resonance spectroscopic imaging

G. Tedeschi, MD; A. Bertolino, MD; A. Righini, MD; G. Campbell, PhD; R. Raman, MD; J.H. Duyn, PhD; C.T.W. Moonen, PhD; J.R. Alger, PhD; and G. Di Chiro, MD

Article abstract—Proton magnetic resonance spectroscopy (^{1}H-MRS) is evolving from single-volume localized acquisitions to multiple-volume acquisitions using magnetic resonance spectroscopic imaging (^{1}H-MRSI). The normal regional patterns of ^{1}H-MRSI-detectable metabolite signal intensities have yet to be established. We studied 13 healthy young adults with a multiple-section ^{1}H-MRSI technique. The metabolite signals measured were *N*-acetylaspartate (NA), choline-containing compounds (CHO), creatine-phosphocreatine (CRE), and lactate. Ten neuroanatomic regions (nine bilateral) were identified in gray matter, white matter, and basal nuclei. Analysis of the data led to the following conclusions: (1) NA and CHO signals from centrum semiovale (CSO) can be used as a normalizing factor to reduce intersubject variability due to external causes; (2) in normal human brain, there is no left versus right asymmetry in the regions studied; (3) statistically significant patterns of signal distribution of NA, CHO, and CRE can be identified in normal human brain; and (4) CSO-normalized metabolite signal intensities and metabolite ratios complement each other for the detection of significant regional differences.

NEUROLOGY 1995;45:1384-1391

Proton magnetic resonance spectroscopy (^{1}H-MRS) is an emerging technique that provides magnetic resonance signals from a number of cerebral metabolites. This technology is presently evolving from single-volume localized ^{1}H-MRS, in which spectral data are acquired from one limited brain volume at a time, to magnetic resonance spectroscopic imaging (^{1}H-MRSI), where spectra from a large number of discrete brain volumes are acquired simultaneously. At present, clinical ^{1}H-MRS measurements are often performed using long echo-time (TE = 272 msec) signal acquisition procedures, which are analogous to those used in T_2-weighted MRI, because these present the least technical demands. The principal metabolite signals detected by ^{1}H-MRSI at long echo time are compounds containing *N*-acetyl, with *N*-acetylaspartate (NA) as the prominent contributor, choline-containing compounds (CHO), creatine-phosphocreatine (CRE), and lactate (LAC). Previous studies[1,2] have suggested that these four metabolite signals, whether acquired by single-volume or spectroscopic imaging approaches, may be valuable in the assessment of certain brain disorders.

The comprehensive description of the normal regional patterns of ^{1}H-MRS–detectable metabolite signal intensities that is necessary for studying brain disorders has yet to be established, mainly because previous studies[3-8] have been performed with large single volumes of interest. For this reason, we studied the regional specificity of signal intensity patterns in the normal brain using a novel multiple-section long-TE ^{1}H-MRSI procedure[9] that permits the simultaneous acquisition of spectra from a great number of small volume elements with a nominal volume resolution of 0.84 ml. To exclude changes in cerebral metabolite signal intensities due to development and aging,[10,11] we deliberately selected only young adult subjects. Our purposes were to (1) document the natural region-to-region variation in metabolite signal intensities; (2) establish whether signal intensities from a variety of brain regions can be effectively normalized to any particular brain region for the purpose of performing comparisons involving multiple subjects;

From the Neuroimaging Branch (Drs. Tedeschi, Bertolino, Righini, Raman, Alger, and Di Chiro) and the Biometry and Field Studies Branch (Dr. Campbell), NINDS, and the In Vivo NMR Research Center (Drs. Duyn and Moonen), NCRR, NIH, Bethesda, MD; and the UCLA Department of Radiological Sciences (Dr. Alger), Los Angeles, CA.

Presented in part at the 46th annual meeting of the American Academy of Neurology, Washington, DC, May 1994.

Received October 19, 1994. Accepted in final form December 6, 1994.

Address correspondence and reprint requests to Dr. Gioacchino Tedeschi, Neuroimaging Branch, NINDS, NIH, Building 10, Room 1C451, 9002 Rockville Pike, Bethesda, MD 20892.

Table 1. Number of ^{1}H-MRSI studies (number of subjects) that had at least one voxel located completely within pairs of anatomic regions in both left and right hemispheres

	CSO	FWM	FC	PC	OC	CING	INS	TH	CD	CV
CSO	20 (13)	14 (9)	18 (13)	12 (9)	18 (13)	11 (10)	16 (10)	13 (8)	14 (10)	9 (8)
FWM		14 (9)	13 (9)	8 (6)	13 (9)	7 (7)	13 (9)	10 (7)	8 (6)	8 (8)
FC			18 (13)	12 (9)	17 (13)	11 (10)	15 (10)	13 (8)	12 (10)	8 (8)
PC				12 (9)	12 (9)	8 (8)	10 (7)	7 (4)	10 (8)	5 (5)
OC					18 (13)	10 (10)	15 (10)	12 (8)	13 (10)	9 (8)
CING						11 (10)	9 (8)	7 (6)	8 (8)	5 (5)
INS							16 (10)	12 (7)	11 (8)	8 (8)
TH								13 (8)	8 (7)	5 (5)
CD									14 (10)	7 (7)
CV										9 (8)

CSO Centrum semiovale. CING Cingulate.
FWM Frontal white matter. INS Insula.
FC Frontal cortex. TH Thalamus.
PC Parietal cortex. CD Caudate.
OC Occipital cortex. CV Cerebellar vermis.

and (3) establish whether any hemispheric asymmetry can be found.

Methods. Thirteen healthy subjects (30 to 40 years of age) participated in the study. Each subject underwent at least one ^{1}H-MRSI examination. Three subjects underwent repeated studies; one subject five times, one subject three times, and one subject two times. Informed consent was given under a human research protocol approved by the appropriate local authority.

Our study was carried out by a multiple-section ^{1}H-MRSI procedure[9] that permits the simultaneous acquisition of spectra from a great number of small volume elements within four 15-mm-thick sections. The acquired data can be displayed in a tomographic format, thus making ^{1}H-MRSI extremely suitable for the study of regional variation of signal intensities. Studies were performed on a 1.5-tesla MR imager equipped with self-shielded gradients (GE Medical Systems, Milwaukee, WI) using a previously described pulse sequence.[9] The standard quadrature imaging head coil was used in all cases. Phase encoding procedures were used to obtain a 32 × 32 array of spectra from volumes having nominal dimensions of 0.84 ml (7.5 mm × 7.5 mm × 15 mm) within the selected sections. The ^{1}H-MRSI sequence comprised a multiple-section spin-echo section selection with a repetition time (TR) of 2,300 msec and TE of 272 msec. Outer-volume signal saturation was used to suppress signals arising from skull marrow and surface tissues. Four 15-mm-thick sections, with a 3.0-mm inter-section gap, were acquired.

Raw ^{1}H-MRSI data were post-processed using software developed at our institution. After Fourier reconstruction, a combination of automated and interactive algorithms was used to identify the location of CHO, CRE, NA, and LAC in spectra from each of the individual voxels within the brain. The magnitude of each acquired spectrum was computed, and the signal strength within 0.05 ppm on either side of the CHO, CRE, NA, and LAC signal positions was integrated to produce four 32 × 32 arrays showing spatial variation of the strength of each of the signals in each of the selected sections. These metabolite spectroscopic images were transferred to a Macintosh computer where they were displayed and subjected to further region of interest (ROI) analysis described below.

Conventional MRIs, collected immediately following the ^{1}H-MRSI acquisition, were used to identify ROIs comprising a defined number of voxels fitting within specific neuroanatomic structures. Relevant sections of the ^{1}H-MRSI signal magnitude images were imported into the Macintosh environment for anatomic correlation with the MRI data. ROIs were drawn on the MRI and then transferred to the identical location on all ^{1}H-MRSIs to obtain all ^{1}H-MRSI signal intensities at this location. Ten neuroanatomic ROIs were identified in gray matter, white matter, and subcortical nuclei. Gray matter ROIs were identified in frontal cortex (FC), occipital cortex (OC), parietal cortex (PC), insula (INS), and cingulate (CING). White matter ROIs were identified in centrum semiovale (CSO) and frontal white matter (FWM). Basal nuclei ROIs were identified in thalamus (TH) and caudate (CD). The tenth ROI was identified in the cerebellar vermis (CV). Each ROI, excepting CV, was obtained from each hemisphere for side-to-side comparison.

A variety of methods was used to calibrate the signal intensities from the different subjects to a common scale. (1) The signal amplitude of each metabolite in each ROI was normalized to the corresponding amplitude in the left CSO (eg, NA-TH/NA-CSO). We used the CSO as a reference because it could be identified in each of the studies and because its raw signals showed the lowest coefficient of variation across the studies (7.1% for NA, 17.2% for CHO, and 31.2% for CRE). (2) Metabolite signal ratios were also calculated from single ROIs (NA/CHO, NA/CRE, CHO/CRE). (3) Left-to-right hemisphere ratios (eg, NA-L-TH/NA-R-TH) were also computed for each ROI.

Although there was a total of 20 studies, we did not use the seven repeated studies (five on the same individual) in the comparison of asymmetries, because the single individual that was the subject in five of the 20 studies could unduly influence the left versus right comparison. The studies that had at least one ^{1}H-MRSI voxel located completely within a particular anatomic ROI in both hemispheres are listed in table 1.

Paired t statistics were used to assess left versus right asymmetry. A multiple-comparison statistical method was employed to assess the regional mean differences of the various calibrated metabolite signal intensities and their ratios. The Bonferroni inequality was used to adjust the p

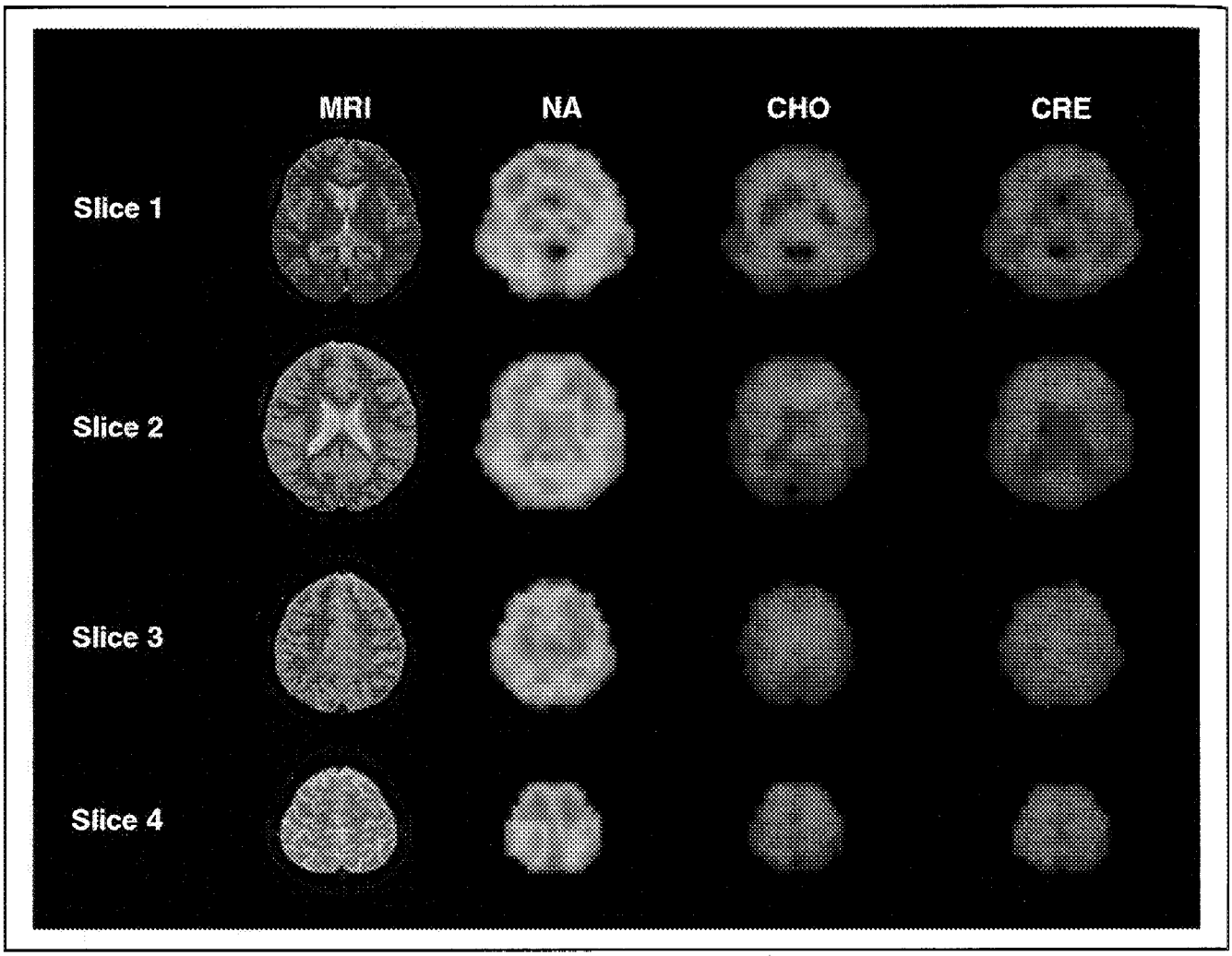

Figure 1. Representative MRIs and N-*acetylaspartate (NA), choline-containing compounds (CHO), and creatine-phosphocreatine (CRE) signal magnitude images of a healthy volunteer at the four selected levels. The 3-mm-thick MR studies correspond to the center of the 15-mm* ^{1}*H-MRSIs.*

values in the reporting of differences so as to preserve the overall experiment error rate at 0.05 for the entire analysis. This analysis comprised all of the regional comparisons for the three metabolites and their ratios, utilized all 20 studies, and included a large number of simultaneous comparisons. For this, we used a general linear model that predicts the mean metabolite (or ratio) difference between two regions allowing for a random effect due to the individual, a random effect for multiple studies within an individual (if available), and an effect due to side (left or right). The statistical software package SAS[12] was used to build the pairwise regional models for each metabolite and each ratio. Both tests for effect of hemispheric asymmetries and for ROI differences were based on an F-test with degrees of freedom that vary as the number of studies common to the two ROIs changes. For the comparison of mean differences between each pair of ROIs, statistical significance is assessed by a statistic that is the difference of the regional means divided by the estimated SE from a general linear model for that pair.

Results. Figure 1 shows characteristic images of NA, CHO, and CRE signal intensities and the corresponding MRIs of one healthy volunteer at the four selected levels.

Figure 2 shows the location of the anatomically defined ROIs (figure 2A) and corresponding spectra (figure 2B) from a characteristic study.

None of the left/right signal intensity ratios in any of the regions were significantly different from 1.0. Group mean left/right signal intensity ratios ranged from 0.99 to 1.04 (SE 0.02 to 0.08) for NA, from 0.86 to 1.12 (SE 0.03 to 0.11) for CHO, and from 0.96 to 1.1 (SE 0.03 to 0.12) for CRE. Thus, there was no evidence of hemispheric asymmetry.

Normative data for the CSO-normalized values of NA, CHO, CRE, and their ratios from the 10 ROIs are reported in table 2. For simplicity the left and right sides were averaged ([left + right]/2). Means and SDs are from 13 separate individuals, using the study with the greatest number of voxels for those who were studied more than once. For CSO-normalized NA, the largest values were found in the white matter, and the smallest in the CD and CV. The SDs from the two white matter ROIs were the smallest ones. For CSO-normalized CHO, the largest values were found in the CV and the

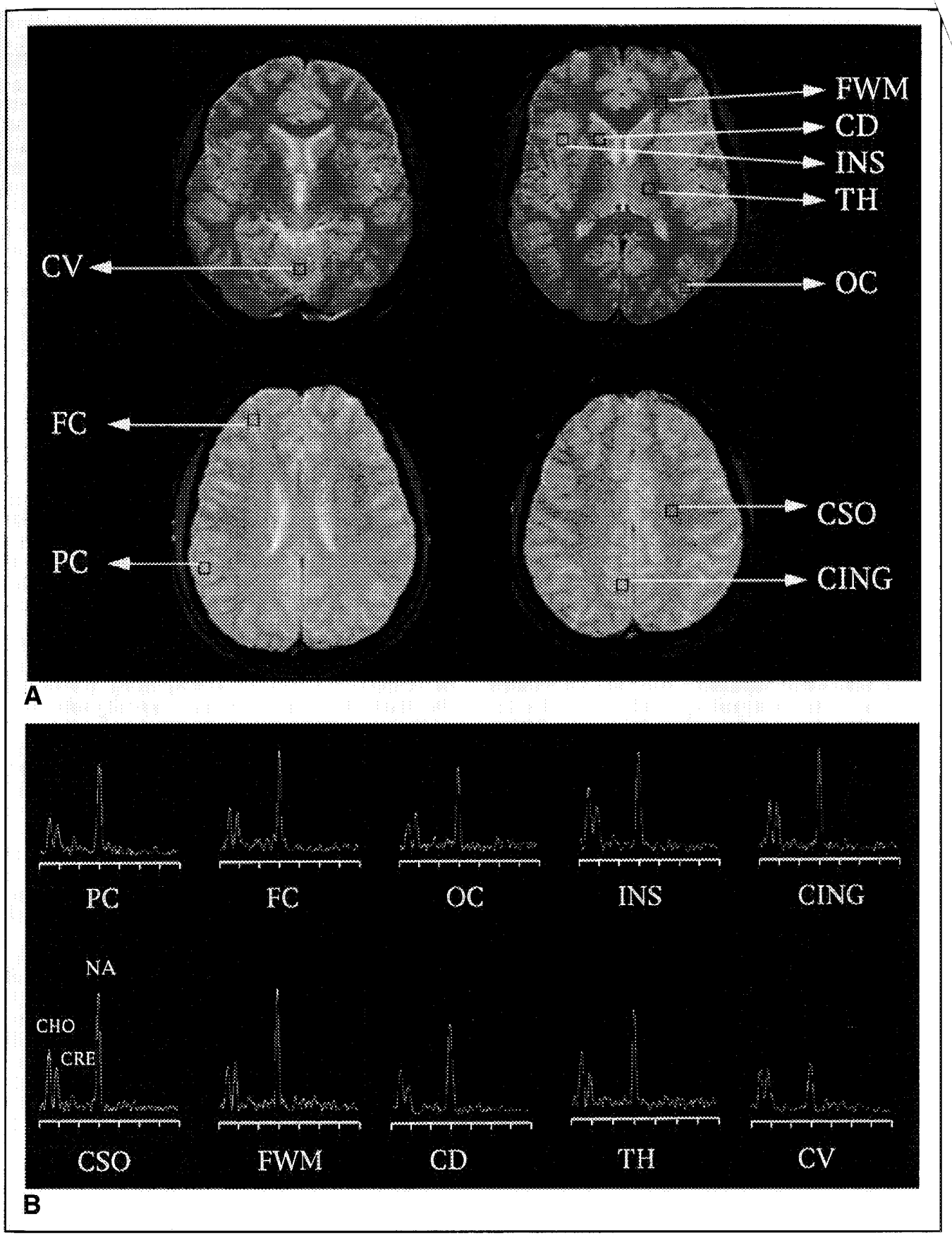

Figure 2. (A) Images depicting the anatomic locations of the 10 selected locations in one of the subjects. The superimposed boxes represent the location and dimensions of individual voxels from the ^{1}H-MRSI array. (B) Magnitude spectra from the different anatomic locations from a single subject. (CV = cerebellar vermis; FC = frontal cortex; PC = parietal cortex; FWM = frontal white matter; CD = caudate; INS = insula; TH = thalamus; OC = occipital cortex; CSO = centrum semiovale; CING = cingulate; NA = N-acetylaspartate; CHO = choline-containing compounds; CRE = creatine-phosphocreatine)

Table 2. Regional distribution of centrum semiovale-normalized metabolite signal intensities and their ratios

ROI	NA		CHO		CRE		NA/CHO		NA/CRE		CHO/CRE	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
CSO	1.004	0.05	0.998	0.06	1.017	0.06	2.334	0.38	3.019	0.6	1.325	0.19
FWM	0.836	0.09	1.068	0.16	1.045	0.25	1.927	0.34	2.819	0.49	1.474	0.11
FC	0.697	0.11	0.79	0.22	0.946	0.35	2.106	0.53	2.337	0.41	1.153	0.2
PC	0.655	0.16	0.563	0.14	0.81	0.15	2.934	0.66	2.6	0.33	0.944	0.14
OC	0.687	0.19	0.549	0.23	0.883	0.25	3.206	0.9	2.431	0.51	0.81	0.23
CING	0.748	0.14	0.899	0.31	1.128	0.24	2.134	0.95	1.997	0.45	1.206	0.28
INS	0.761	0.19	1.231	0.39	1.494	0.66	1.537	0.37	1.759	0.44	1.141	0.23
TH	0.793	0.19	0.968	0.29	1.035	0.31	1.911	0.42	2.316	0.54	1.272	0.24
CD	0.554	0.11	0.915	0.22	1.082	0.38	1.514	0.47	1.68	0.41	1.146	0.3
CV	0.602	0.21	1.375	0.59	1.799	0.87	1.053	0.13	1.312	0.25	1.032	0.2

For region of interest (ROI) abbreviations, see table 1. With the exception of CV, reported values are equal to (left + right)/2.

NA *N*-Acetylaspartate.
CHO Choline-containing compound.
CRE Creatine-phosphocreatine.

smallest in the OC and PC. For CSO-normalized CRE, the largest value was found in the CV and the smallest in the OC, PC, and FC. For NA/CHO, the largest values were found in the OC and PC, and the smallest in the CV. For NA/CRE, the largest value was found in the CSO and the smallest in the CV. For CHO/CRE, the largest values were found in the white matter and the smallest in the OC and PC.

Two tables with detailed results have been filed with the National Auxiliary Publications Service (see Note at the end of the text). Each pair of ROIs that has statistically significantly different means (as obtained by the regional mean difference divided by the estimated SE) is indicated using asterisks in these tables. For significant pairs, the numeric entries in the tables are not the above statistics but the mean regional differences divided by the estimated SD from the pairwise general linear model. This measures distance of the regional means but is insensitive to varying number of subjects for each pair of ROIs.

CSO-normalized NA. The mean CSO value was significantly larger than all other ROIs except FWM. The mean FWM produced significantly larger values than the gray matter ROIs FC, PC, and OC as well as CD and CV. PC and CD means were significantly smaller than INS and TH.

CSO-normalized CHO. The mean CSO produced significantly larger values than FC, PC, and OC. The mean FWM produced a significantly larger value than PC, OC, and FC. Some significant intra-gray matter differences were found. The TH and CD means were significantly larger than some gray matter ROIs.

CSO-normalized CRE values. The INS mean was significantly larger than white matter and the gray matter ROIs FC, PC, and OC, as well as basal nuclei.

Ratio NA/CHO. The OC mean was significantly larger than white matter, FC, INS, TH, CD, and CV. Also, both CD and INS means were significantly smaller than CSO, FC, and PC. Some significant intra-gray matter differences were found. The CV mean was significantly smaller than white matter and FC.

Ratio NA/CRE. The CSO mean was significantly larger than FWM, the gray matter ROIs FC, OC, CING, and INS, as well as basal nuclei and CV. Both CD and CV means were significantly smaller than FWM, FC, and OC.

Ratio CHO/CRE. White matter ROI means were significantly larger than some gray matter ROIs, some significant intra-gray matter differences were found, and CV mean was significantly smaller than FWM.

No detectable LAC signal was found in our group of healthy adult volunteers. This finding is consistent with the normal intracerebral LAC concentration (about 0.5 μmol/g) being close to or below the present detection limit of the method.

A preliminary study of the variability from repeated studies using the 10 multiple studies of three subjects (one with five studies, one with three, and one with two) showed that the variability was much smaller within than between individuals for NA and NA/CRE. The ratio of between to within variance was always less than 1 for the latter measures, but appeared to vary considerably for the different ROIs in our small sample of repeated-study investigation.

Discussion. Many reports[3-8] deal with the determination of absolute metabolite concentrations in normal human brain by ^{1}H-MRS. Frahm et al[5] studied the concentrations of ^{1}H-MRS–detectable cerebral metabolites from selected 27- and 64-ml volumes of interest localized in the insular area, the occipital

area, the thalamus, and the cerebellum of normal volunteers. Michaelis et al[6] measured absolute concentrations with volumes of interest of 2.7 to 18 ml in parietal white matter, parietal gray matter, cerebellum, thalamus, and pons. In these papers, however, the regional variation in the signal intensities has not been systematically addressed, because the research had been carried out with large volumes of interest and single-voxel technique. The ^{1}H-MRSI method we used here provides better spatial resolution, permitting more detailed examination of regional variation, but it does not lend itself to absolute quantitation. We have focused, therefore, on regional signal intensity patterns and have empirically defined "normal" patterns of metabolite signal intensities so that these can be used as standards of normality when studying brain disorders.

The ^{1}H-MRSI technique is designed only to provide "ratio measures" of signal intensities. These ratio measures can be of two types: (1) the intensity of a particular metabolite signal at one anatomic location relative to that of the same metabolite signal at another anatomic location, and (2) the amplitude of one metabolite signal from one anatomic location relative to the amplitude of another metabolite signal at the same location. Ratios of the latter type have been used extensively in previous MRS studies of the brain because the majority of such studies used single-volume acquisition. These ratios also may magnify certain types of abnormalities. For instance, Meyerhoff et al[13] reported that a reduction of NA/CHO and NA/CRE, together with normal CHO/CRE, in the white matter of patients with Alzheimer's disease is indicative of axonal injury. Ratios of the first type, which can only be acquired by multivoxel procedure, provide a means of calibrating data from different subjects to a common scale for intrasubject comparisons. In the present study, we assessed a number of possible ratio calibration procedures, and found that ratios of the second type are complementary to ratios of the first type.

Absence of side differences. An important finding was that no left versus right asymmetry was evident either by direct analysis of the nine regions in the 13 individuals or by the general linear model analysis of the 20 studies. There is a possibility that asymmetries exist in regions not included in the nine bilateral ROIs that were studied. However, the overwhelming statistics from these nine ROIs suggest that this is unlikely. The absence of left versus right asymmetry is of paramount importance for the applicability of ^{1}H-MRSI to focal brain pathology (eg, brain tumors) because it supports the validity of using the region contralateral to a brain lesion as an internal reference without regard for which hemisphere is affected.

Intersubject variability. A second relevant finding is the low intersubject variability in the raw uncalibrated signal intensities from the CSO. The coefficients of variation for the uncalibrated signals from this region were 7.1% for NA and 17.2% for CHO. This illustrates that NA and CHO signals from the CSO are highly suitable as calibration factors to be used to reduce intersubject variability arising from technical causes. An alternative approach to reduce intersubject variability is the use of ratio of pairs of metabolite signals arising in a single volume.

A preliminary reproducibility study using the repeated studies of three subjects showed that the variability was much smaller within than between individuals for NA and NA/CRE. However, this analysis is highly dependent on only a few subjects with repeated studies, and one individual constituted half of the multiple studies. A more extensive study is underway to assess systematically the reproducibility of this ^{1}H-MRSI.

When using, as we did, long-TE acquisition procedures, the signal intensities are dependent on T_2 values as well on the local metabolite concentration. Thus in interpreting any regional pattern one must keep the two parameters in mind. Either parameter may depend on something as simple as the cellular composition of the region under examination. Thus the regional patterns we have observed may simply reflect variations of gray matter/white matter ratio in the different regions.

NA distribution. Our study revealed an unexpected statistically significant NA signal intensity pattern that has clinical implications. NA is inferred to be a neuron-specific molecule because it is present largely, if not entirely, within neurons,[14,15] being absent in both mature glial cultures and tumors of glial origin.[16-19] In the white matter, the NA signal must therefore arise from within the axons. Since the axonal component does not constitute a large fraction of the white matter space,[20] cerebral gray matter should produce a stronger NA signal than white matter. Our results indicate that the NA signal intensity is significantly larger in white matter than it is in either cortical or the basal nuclei gray matter. This finding may be related to a longer NA T_2 value in the white than in the gray matter.[5] On the other hand, other *N*-acetyl moieties that could have relatively higher white matter concentration[21] may contribute to the higher NA signal found in the white matter.

Our data also demonstrate that the NA signal is homogeneously distributed within the cortical gray matter. The only significant intra-gray matter difference we found was that the INS produces a significantly larger signal than the PC. A significant intra-nuclei difference was observed, the TH producing a significantly larger signal than the CD. Finally, the CV shows a significantly smaller signal than the white matter, this finding being in agreement with the absolute NA concentration values reported by Michaelis et al.[6]

CHO distribution. The CHO signal comprises a variety of compounds that contain trimethylamine groups. Miller[22] speculates that the CHO peak includes contributions from non–water-extractable compounds. A recent in vivo and in vitro study[23] of canine brain has attributed the CHO peak predom-

inantly to glycerophosphocholine and phosphocholine. The CHO signal increases in multiple sclerosis because of myelin breakdown[24-26] and in brain tumors because of changes in turnover of membrane constituents.[27] Furthermore, in brain tumors, necrotic portions and areas of radiation necrosis show decreased CHO signals.[27] Our finding that the CV produces the highest CHO value, as well as that the white matter produces a higher value than the gray matter, is in agreement with absolute CHO values reported by Frahm et al.[5]

CRE distribution. In vivo ^{1}H-MRSI measures creatine and phosphocreatine together as a single signal. Because of that, it is difficult to attribute differences in CRE signal intensities to local derangements of energy metabolism. The CRE signal amplitude is more likely a measure of local tissue density. Brain tumors,[22,27] abscesses,[22] and infarctions[28] produce alterations of CRE signal intensity. Our finding that the CV produces the highest CRE signal intensity is in agreement with measurements of absolute concentration.[6] Furthermore, our data show that even though CRE signal does not vary as much as NA and CHO, it is not distributed homogeneously within the brain. Therefore, the use of CRE signal intensity as an internal intensity standard without regard for anatomic location may be of limited value.

While this manuscript was undergoing review, Hetherington et al[29] published a ^{1}H-MRSI study about cerebral gray and white matter metabolite differences. After correction for T_1 and T_2 losses, NA was significantly higher in white matter, while CRE was significantly lower in white matter. Any discrepancies between our results and theirs may be related to the fact that we report ratios without correction for T_1 or T_2 losses, to our use of a different field strength, or to differences in choice of the ROIs.

Conclusions. ^{1}H-MRSI has several limitations that must be considered. The relative low concentration of detectable metabolites limits the spatial and temporal resolution. The imaging and reconstruction procedures used in ^{1}H-MRSI introduce some uncertainty in defining the exact edges of the voxels. The spectra from any one voxel have small contamination from the adjacent voxels. For this reason the term "nominal" is used when the volume of resolution is specified. The 15-mm section used in ^{1}H-MRSI limits the number of anatomic regions that can be studied. We were able to identify only a limited number of structures that spanned as much as 15 mm. The signal-to-noise considerations make it very hard to reduce the acquisition time to an amount that will eliminate the problem of the subject's motion. Despite that, the metabolic information that can be acquired in vivo makes ^{1}H-MRSI a promising method for the assessment of certain CNS disorders. The color spectroscopic images shown herein do not offer anatomic resolution similar to conventional MRI. Nevertheless, they represent an improvement toward the use of ^{1}H-MRSI in the study of CNS disorders.

The clinical interpretation of such images requires that spectroscopic imaging data from normal subjects be established. In this paper we carried out an analysis of the normal metabolite distribution patterns as demonstrated by ^{1}H-MRSI. The statistical results lead to the following conclusions: (1) NA or CHO signals from CSO can be used as a normalizing factor to reduce intersubject variability due to external causes; (2) in normal human brain there is no left versus right asymmetry in the regions studied; (3) statistically significant patterns of signal distribution of NA, CHO, and CRE can be identified in normal human brain; and (4) CSO-normalized metabolite signal intensities and metabolite ratios are complementary for detecting significant regional differences.

Note. Readers can obtain two supplementary tables (two pages) from the National Auxiliary Publications Service (NAPS), c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, NY 10163-3513. Request document no. 05815. Remit with your order (not under separate cover), in US funds only, $7.75 for photocopies or $4.00 for microfiche. Outside the United States and Canada, add postage of $4.50 for the first 20 pages and $1.00 for each 10 pages of material thereafter, or $1.75 for the first microfiche and $.50 for each fiche thereafter. *There is a $15.00 invoicing charge on all orders filled before payment.*

References

1. Prichard JW, Brass LM. New anatomical and functional imaging methods. Ann Neurol 1992;32:395-400.
2. Bottomley PA. The trouble with spectroscopy papers. J Magn Reson Imaging 1992;2:1-8.
3. Alger JR, Symko SG, Bizzi A, Posse S, DesPres DJ, Armstrong MR. Absolute quantitation of short TE brain ^{1}H-MR spectra and spectroscopic imaging data. J Comput Assist Tomogr 1993;17:191-199.
4. Narayana PA, Johnston D, Flamig DP. In vivo proton magnetic resonance spectroscopy studies of human brain. Magn Reson Imaging 1991;9:303-308.
5. Frahm J, Bruhn H, Gyngell ML, et al. Localized proton NMR spectroscopy in different regions of human brain in vivo: relaxation times and concentrations of cerebral metabolites. Magn Reson Med 1989;11:47-63.
6. Michaelis T, Merboldt KD, Bruhn H, Hanicke W, Frahm J. Absolute concentrations of metabolites in the adult human brain in vivo: quantification of localized proton MR spectra. Radiology 1993;187:219-227.
7. Christiansen P, Henriksen O, Stubgaard M, Gideon P, Larsson HBW. In vivo quantification of brain metabolites by ^{1}H-MRS using water as an internal standard. Magn Reson Imaging 1993;11:107-118.
8. Hennig J, Pfister H, Ernst T, Ott D. Direct absolute quantification of metabolites in the human brain with in vivo localized proton spectroscopy. NMR Biomed 1992;5:193-199.
9. Duyn JH, Gillen J, Sobering G, van Zijl PC, Moonen CTW. Multisection proton MR spectroscopic imaging of the brain. Radiology 1993;188:277-282.
10. van der Knaap MS, van der Grond J, van Rijen PC, et al. Age-dependent changes in localized proton and phosphorus MR spectroscopy of the brain. Radiology 1990;176:509-515.
11. Bruhn H, Stoppe G, Merboldt KD, Michaelis T, Hanicke W, Frahm J. Cerebral metabolic alterations in normal aging and Alzheimer's dementia detected by proton magnetic resonance spectroscopy [abstract]. In: Book of abstracts. Society of Magnetic Resonance in Medicine 1992. Berkeley, CA: Society of Magnetic Resonance in Medicine, 1992:752.
12. Statistical Analysis System. SAS/STAT user's guide (version 6, 4th ed). Cary, NC: SAS Institute, 1989:891-996.
13. Meyerhoff DJ, MacKay S, Constans JM, et al. Axonal injury and membrane alterations in Alzheimer's disease suggested

by in vivo proton magnetic resonance spectroscopic imaging. Ann Neurol 1994;36:40-47.
14. Tallan HH. Studies on the distribution of *N*-acetyl-L-aspartic acid in brain. J Biol Chem 1957;224:41-45.
15. Koller JK, Zaczek R, Coyle JT. *N*-Acetyl-aspartyl-glutamate: regional levels in rat brain and the effects of brain lesions as determined by a new HPLC method. J Neurochem 1984; 43:1136-1142.
16. Birken DL, Oldendorf WH. *N*-Acetyl-L-aspartic acid: a literature review of a compound prominent in ^{1}H-NMR spectroscopic studies of brain. Neurosci Biobehav Rev 1989;13:23-31.
17. Urenjak J, Williams SR, Gadian DG, Noble M. Proton nuclear magnetic resonance spectroscopy unambiguously identifies different neural cell types. J Neurosci 1993;13:981-989.
18. Peeling J, Sutherland G. High-resolution ^{1}H NMR spectroscopy studies of extracts of human cerebral neoplasms. Magn Reson Med 1992;24:123-136.
19. Gill SS, Thomas DG, Van Bruggen N, et al. Proton MR spectroscopy of intracranial tumors: in vivo and in vitro studies. J Comput Assist Tomogr 1990;14:497-504.
20. Hanstock CC, Rothman DL, Prichard JW, Jue T, Shulman RG. Spatially localized ^{1}H NMR spectra of metabolites in the human. Proc Natl Acad Sci USA 1988;85:1821-1825.
21. McIlwain H, Bachlelard HS. Biochemistry and the central nervous system. 5th ed. Edinburgh: Churchill Livingstone, 1985:314.
22. Miller BL. A review of chemical issues in ^{1}H NMR spectroscopy: *N*-acetylaspartate, creatine and choline. NMR Biomed 1991;4:47-52.
23. Barker PB, Breiter SN, Soher BJ, et al. Quantitative proton spectroscopy of canine brain: in vivo and in vitro correlations. Magn Reson Med 1994;32:157-163.
24. Arnold DL, Matthews PM, Francis G, Antel J. Proton magnetic resonance spectroscopy of human brain in vivo in the evaluation of multiple sclerosis: assessment of the load of disease. Magn Reson Med 1990;14:154-159.
25. Larsson HBW, Christiansen P, Jensen M, et al. Localized in vivo proton spectroscopy in the brain of patients with multiple sclerosis. Magn Reson Med 1991;22:23-31.
26. Arnold DL, Matthews PM, Francis G, et al. Proton magnetic resonance spectroscopic imaging for metabolic characterization of demyelinating plaques. Ann Neurol 1992;31:235-241.
27. Fulham MJ, Bizzi A, Dietz MJ, et al. Mapping of brain tumor metabolites with proton MR spectroscopic imaging: clinical relevance. Radiology 1992;185:675-686.
28. Duijn JH, Matson GB, Maudsley AA, et al. Human brain infarction: proton MR spectroscopy. Radiology 1992;183:711-718.
29. Hetherington HP, Mason GF, Pan JW, et al. Evaluation of cerebral gray and white matter metabolite differences by spectroscopic imaging at 4.1 T. Magn Reson Med 1994; 32:565-571.

Seizure-like discharges recorded in human dysplastic neocortex maintained in vitro

Donatella Mattia, MD; André Olivier, MD, PhD; and Massimo Avoli, MD, PhD

Article abstract—Application of the convulsant drug 4-aminopyridine (50 to 100 μM) induced spontaneous seizure-like discharges (duration = 76.3 ± 46.8 sec, mean ± SD; interval of occurrence = 225.2 ± 87.9 sec) in slices of neocortex obtained from patients with a diagnosis of focal neuronal migration disorders during neurosurgical procedures for relief of drug-resistant seizures. Similar epileptiform discharges could also be elicited in these slices by single-shock stimuli delivered in the underlying white matter or within the gray matter. By contrast, neocortical slices obtained from patients suffering from temporal lobe epilepsy (which is characterized by Ammon's horn sclerosis but relatively normal neocortex) did not generate any epileptiform activity during 4-aminopyridine application. Thus, our study is the first to provide experimental evidence for the intrinsic epileptogenicity that characterizes neuronal migration disorders.

NEUROLOGY 1995;45:1391-1395

Neuronal migration disorders (NMDs) represent a broad variety of congenital abnormalities of the cortical cytoarchitectonic organization that includes major dysgenesis as well as focal cortical dysplasia.[1-6] Several clinical studies have revealed that severe partial epilepsy resistant to conventional anticonvulsant therapy represents the major and most frequently encountered manifestation among the neurologic syndromes associated with NMDs.[6-9] In young patients with focal NMDs and intractable

From the Montreal Neurological Institute, the Department of Neurology and Neurosurgery, and the Department of Physiology, McGill University, Montreal, PQ, Canada.

Supported by the MRC of Canada (MT-8109) and the Hospital for Sick Children Foundation (XG93-056). M.A. is an FRSQ Chercheur-Boursier Senior. D.M. is a fellow of Fondazione per la Ricerca Sulla Epilessia (FOREP) and of the Savoy Foundation.

Received July 26, 1994. Accepted in final form December 6, 1994.

Address correspondence and reprint requests to Dr. Massimo Avoli, Montreal Neurological Institute, 3801 University, Montreal, QC, Canada H3A 2B4.